Title: **OB/GYN Department Deliveries**	**Policy**

POLICY STATEMENT:
This protocol serves as a guide for decision-making for administration of antenatal corticosteroids (ACS: betamethasone) to women at risk of late preterm birth (34 0/7 – 36 6/7 weeks gestation). Clinicians may deviate from these guidelines in individualizing treatment for certain patients who desire ACS who do not meet the guideline criteria, with appropriate informed consent. Current guidance for administering ACS to women at risk of preterm delivery prior to 34 weeks remains unchanged.

The Antenatal Late Preterm Steroids (ALPS) study was published in February 2016, which showed that when women at risk for late preterm delivery are given ACS, their newborns require less respiratory intervention in the first 72 hours of life.[1] The question of whether ACS in the late preterm period confer any neonatal benefit has long been an area of uncertainty, and this study is the first whose design and statistical power have shown real benefit. Its publication has prompted a new statement by SMFM supporting the use of ACS and is already leading to widespread change in clinical practice. Both the ALPS study, the SMFM guidelines, and the available evidence are summarized below.

PURPOSE:
1. To review known benefits of ACS
2. To review current evidence driving the practice of administering ACS in the late preterm period
3. To review known potential harms of ACS
4. To review recommendations for late preterm ACS published by the Society for Maternal-Fetal Medicine (SMFM)
5. To derive late preterm ACS practice recommendations from evidence-based reviews
6. To allow the maximum number of infants to benefit while minimizing exposure to potential harms
7. To simplify the decision-making process for clinicians presented with urgent clinical situations.

SCOPE:
Population: All pregnant women at risk of preterm delivery from 34 0/7 – 36 6/7 weeks gestation.

SUMMARY:
In the late preterm period, benefits conferred by ACS are modest (2.8% Absolute Risk Reduction (ARR) in primary outcome of 2-4 hours of CPAP/high-flow nasal cannula (NC) or supplemental

02) and are comparable to the calculated risks of adverse neurologic effects of ACS. However, compared to the modest clinical significance and brevity of the demonstrated reduction in the need for non-invasive respiratory support in the ALPS trial, the gravity and long-term implications of the potential neurologic risks are potentially much more significant (2.0% ARI for neurosensory disability, 2.8% ARI in decreased school performance, and unquantified but persistently altered cortisol response to stressful stimuli). Given the balance of risks and benefits, more restrictive criteria for the use of ACS than endorsed by SMFM are suggested in this guideline.

RECOMMENDATIONS:

- Administer ACS to women with an **indicated delivery** in the late preterm period (34 0/7 to 36 6/7 weeks gestation), betamethasone: 2 doses of 12mg IM, 24 hours apart. Examples of indicated delivery include but are not limited to:
  - Hypertensive disorder
  - Abnormal placentation
  - PPROM
  - IUGR
- Administer ACS to women with evidence of preterm labor (cervical dilation at least 3 cm or effacement at least 75%) **no later than 35 6/7 weeks.**
- Do not use tocolytics in the late preterm period to "buy time" to complete the steroid course.
- Do not give ACS to women with a potential medical indication for late preterm delivery until a definitive plan is in place for indicated late preterm delivery.
- Continue the practice of standardized screening of neonates born in the late preterm per for neonatal hypoglycemia, as per the NICU/ICN protocol.
- Do not give ACS for conditions not studied in the ALPS trial. Exclusion criteria are listed in Appendix A.

Detailed summary of available evidence including benefits and risks of ACS in the late preterm period:

- In February 2016, the Antenatal Late Preterm Steroids (ALPS) study was published, the first large trial to evaluate the effects of ACS for women at risk of **late preterm delivery** (34 0/7- 36 6/7 wks)[1]. Summary of study design and findings:
  - RCT of betamethasone vs placebo for women at risk of preterm delivery between 34 0/7 – 36 6/7 weeks' gestation. N= 2827, powered to detect a 33% reduction of primary outcome, assuming a baseline risk of 9.5%. Analysis by intention-to-treat.
  - Inclusion criteria: High risk for preterm delivery (PPROM, preterm labor (at least 3cm dilated **or** 75% effaced), or any other indication or diagnosis requiring delivery in the next 1-7 days).
  - Exclusion criteria:
    - Prior course of ACS
    - Likely to deliver in <12hrs
    - Chorioamnionitis

        - Cervix ≥ 8cm dilated
        - Poor dating (known LMP but earliest US >32wks or LMP unknown and earliest US >24wks)
    - Primary outcome: composite for neonatal respiratory support in first 72hrs of life:
        - CPAP of high-flow nasal cannula for ≥ 2 consecutive hours
        - Supplemental 02 with Fi02 ≥ 30% for 4 continuous hours
        - ECMO
        - Mechanical ventilation
        - Fetal/neonatal death

    - Results: Compared with placebo, ACS group had:
        - lower rate of primary composite outcome (11.6% vs 14.4%) and several respiratory complications (all with $p < 0.05$): TTN, BPD, need for resuscitation at birth, surfactant use, composite of RDS/TTN/apnea, NICU admission >3days
        - Higher rate of neonatal hypoglycemia
        - No difference in rates of: RDS, NEC, IVH, length of stay, NICU admission, sepsis, birth weight,
        - 16% of women enrolled went on to deliver at term.

Benefits, as found in ALPS study:

- Reduced need for respiratory support in first 72 hours of life
    - Lower rate of primary composite outcome (CPAP/high-flow NC for ≥ 2 consecutive hours, supplemental 02 with Fi02 ≥ 30%, ECMO, mechanical ventilation, fetal/neonatal death). Note: no deaths or use of ECMO occurred in the study)
    - Reduced need for any resuscitation at birth, surfactant use, NICU admission >3 days
- Reduced respiratory complications: TTN, BPD, composite of RDS/TTN/apnea

Risks:

- There is extensive literature on ACS using various animal models showing adverse effects on brain development. Examples:
    - Single dose of ACS in sheep reduced brain weight at term by 10%[3]
    - Repeated ACS doses delay optic and sciatic nerve myelination[4–6]
    - ACS inhibits neuronal development in primates[7]
- While ACS have not been shown to have long-term adverse effects among infants born preterm, there is evidence that human infants whose mothers receive ACS but deliver at term are at risk for adverse outcomes:
    - 5 year follow up from the MACS trial[8], the largest RCT (n=1853) to evaluate the use of repeat ACS courses, showed that infants given even a single course of ACS who delivered at term had a 3.7-fold increase of neurosensory disability (absolute risk increase of 6.8%).

    - Long-term follow up from the ASTECTS trial, a RCT of ACS for scheduled cesarean delivery at term, showed that children ages 8-15 who had received ACS were twice as likely (9.2% absolute risk increase) to receive the designation of "lower quarter of academic ability" in an educational assessment.
    - Women who received ACS who delivered at term had children with higher cortisol responses to standardized stress stimuli at age 6-11 compared with children whose mothers had not received ACS.[9]
- Multiple RCTs testing the use of ACS have reported that approximately 30% of study participants deliver at term[8,10]. In the ALPS study[1], only 16% of study participants delivered at term. This low rate was likely due to very strict inclusion criteria, which are unlikely to be applied rigorously in routine clinical practice, and which suggest that the historical rate of 30% is more likely.
- In order to approximate the prospective risk of neurologic harm in an infant whose mother receives ACS due to concern for preterm delivery, the following are assumed:
    - A 30% probability of delivery at term, consistent with historical rates
    - Infants of mothers given ACS who deliver at term will suffer:
        - 6.8% absolute risk increase of neurosensory disability x 30% risk of term delivery = 2.0% absolute risk increase
        - 9.2% absolute risk increase of adversely affected school performance x 30% risk of term delivery = 2.8% absolute risk increase
- Following publication of the ALPS study, SMFM published a statement in support of ACS in the late preterm period, summarized here:[11]
    - Use of ACS is recommended for women in the late preterm period who are at high risk for delivery within the next 7 days or before 37 weeks.
    - Women with symptoms of preterm labor should not be given ACS until there is evidence of preterm labor: cervical dilation at least 3cm or effacement at least 75%.
    - Tocolysis is not recommended to complete the steroid course in women in the late preterm period.
    - In women with a potential indication for late preterm delivery, ACS should not be given until a definitive plan is in place for late preterm delivery.
    - Institutions should use standardized guidelines for assessment and management of neonatal hypoglycemia.
    - ACS in the late preterm period should not be used in populations not included in the ALPS trial.

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11. SMFM late preterm ACS statement 3.

APPENDIX A:

ALPS study Exclusion criteria:

1. Any prior course of corticosteroids during the current pregnancy
2. Candidate for stress dose steroids because of chronic steroid therapy
3. Twin gestation reduced to a singleton gestation at or after 14 weeks 0 days either spontaneously or therapeutically
4. Known major fetal anomaly, including cardiac anomaly and hydrops, or two or more minor fetal anomalies
5. Maternal contraindication to betamethasone: hypersensitivity reaction, ITP, systemic fungal infection, use of amphotericin B
6. Pre-gestational diabetes
7. Chorioamnionitis

APPROVAL

Prepared by: Division of MFM

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Approval: Eve Espey, MD, MPH  6/16/2016
Chair, Department of Obstetrics & Gynecology Date

SOP # / Version #	Effective Date	Supersedes	Review Date	Summary of Change(s)